UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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OFFICE OF
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AND TOXIC SUBSTANCES

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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
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MEMORANDUM

SUBJECT: Dicamba: Human-Health Risk Assessment for Proposed Section 3 New Uses on Sweet Corn.
Petition No. 0E6209
PC Code: 029801 DP: 340156 Decision: 304187

Regulatory Action Type: Section 3 Registration
Risk Assessment Type: Single Chemical/Aggregate

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The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. The RD of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed (and registered) uses of dicamba in/on sweet corn.

A summary of the findings and an assessment of human-health risk resulting from the proposed and registered uses of dicamba are provided in this document. The residue chemistry review was provided by George Kramer (RAB1), the dietary exposure assessment was provided by Sarah Levy (RAB1), the hazard assessment was provided by P.V. Shah, and the risk assessment was provided by Mary Clock-Rust (RAB1). The hazard characterization and the occupational and residential exposure assessments were taken from the dicamba reregistration eligibility document (RED) (Memo, C. Olinger, D317720, 9/13/2005).

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1.0 Executive Summary

Dicamba (3,6-dichloro-o-anisic acid) is a selective benzoic acid herbicide registered for the control of certain broadleaf weeds and woody plants before their emergence. It is an auxin agonist that is readily translocated symplastically and apoplastically with accumulation in meristemic regions of the plant. Sensitive plants exhibit rapid uncontrolled growth characterized by twisting and curling of stems and petioles, stem elongation and swelling and leaf cupping. Weed control is generally achieved in 5 to 7 days.

Different forms of dicamba (acid and salt) have registered uses on rights of way areas, asparagus, barley, corn (field and pop), grasses grown in pasture and rangeland, oats, proso millet, rye, sorghum, soybeans, sugarcane, and wheat. There are residential uses on turf and ornamentals. Application rates range from 0.5 to 2.8 lb ae (acid equivalent)/A.

A RED document was issued by HED on September 13, 2005 (Memo, C. Olinger, D317720). Some sections of the RED have been summarized in this document. For detailed information on dicamba, please refer to the RED.

The current petition (0E6209) is a proposal for tolerances on sweet corn, forage and stover. A summary of the scientific databases and estimated risks from the proposed use are included in this memorandum.

Hazard Assessment Summary
Dicamba has a low acute toxicity via oral, dermal or inhalation route (Acute Toxicity Category 3 or 4). It is an eye and dermal irritant but it is not a skin sensitizer. Consistent neurotoxic signs (e.g., ataxia, decreased motor activity, impaired righting reflex and gait) were observed in many studies in rats and rabbits at high doses. There was an increased incidence of abortion in the rabbit developmental toxicity study at doses that also showed maternal toxicity. In a two-generation reproductive toxicity study, offspring toxicity was manifested as decreased pup body weight gain in all generations at a dose lower than the parental systemic toxicity no-observed adverse-effect level (NOAEL). Developmental studies in rats and rabbits showed no evidence (qualitative or quantitative) for increased susceptibility following in utero and/or pre-/post-natal exposure. Following oral administration, dicamba is rapidly absorbed and excreted in urine and feces. Dicamba is classified as "not likely to be carcinogenic to humans." Mutagenicity studies did not demonstrate evidence of mutagenic potential for dicamba although some positive results were reported in published literature.

Dose-Response Assessment
An acute neurotoxicity study in rats was selected for the general population, including infants and children, as the basis for an endpoint of concern for acute dietary risk assessment. For short- and intermediate-term incidental oral exposure and the chronic reference dose (cRfD), a multi-generation reproductive toxicity study in rats was selected based on impaired pup growth (decreased pup weights).

The dose and endpoint selected for dermal and inhalation risk assessment for all durations was based on a multi-generation reproductive toxicity study in rats. The multi-generation

reproductive toxicity study with a longer duration and a NOAEL of 45 mg/kg/day is protective and appropriate for short-, intermediate- and long-term dermal risk assessments. The 28-day dermal toxicity study in rats was not selected for dermal risk assessment because the offspring effect in the reproductive toxicity study was not measured in this study. In addition, the NOAEL (1000 mg/kg/day) in the 28-day dermal toxicity study would not be protective of the reproductive-offspring effects in the rat multi-generation reproductive toxicity study with a NOAEL of 45 mg/kg/day using a dermal-absorption factor of 15%. Since an oral NOAEL was selected, a 15% dermal-absorption factor was used for route-to-route extrapolation for assessing dermal risk.

Food Quality Protection Act (FQPA)

There is no evidence of increased qualitative or quantitative susceptibility following *in utero* exposure in the developmental toxicities in rats and rabbits. There was evidence of increased quantitative susceptibility to the offspring following pre- / postnatal exposure in the two-generation reproduction study in rats. In that study, offspring toxicity was manifested as decreased pup body weight gain in all generations at a dose lower than the parental systemic toxicity NOAEL. However, the NOAEL of 45 mg/kg/day identified in this study was chosen for risk assessments for all routes and exposure durations other than acute oral exposures. Since this NOAEL is the lowest (most sensitive endpoint) in the dicamba toxicity data base, and the dose-response observed in the study is well defined assuring that this dose is a clear NOAEL, use of the NOAEL and endpoint for risk assessment is protective for all observed toxic effects of the chemical. Therefore, there is low concern for the increased susceptibility observed in the reproduction study since all appropriate risk assessments utilize this endpoint. Additionally, there is no increased susceptibility observed in the developmental toxicity studies.

Levels of Concern

The uncertainty factors (UFs) used in determining the acute and chronic RfD exposure limits were 100x (10x for intraspecies variation and 10x for interspecies extrapolation). In addition to the 10x UF for intraspecies variation and the 10x UF for interspecies extrapolation, an additional 3x was applied to the acute dietary risk assessment for general population for using a LOAEL in establishing the acute reference dose (aRfD).

For all non-dietary risk assessments, HED's level of concern (LOC) is a margin of exposure (MOE) of 100 (10x UF for intraspecies variation and 10x UF for interspecies extrapolation).

Dietary Exposure

Several plant metabolism studies have been submitted for dicamba. Generally there are two major plant metabolites 3,6-dichloro-5-hydroxybenzoic acid (5-OH dicamba) and 3,6-dichlorosalicylic acid (DCSA), which are structurally similar to the parent compound and are included in the dietary risk assessment.

Tolerance-level residues, Dietary Exposure Evaluation Model (DEEM-FCID™), Version 7.76 default processing factors, and 100 percent crop treated (CT) data were used in the acute and chronic dietary assessments. For both acute and chronic dietary assessments, the general U.S. population and all population subgroups have risk estimates which were not of concern to HED. For the acute assessment, the most highly exposed population subgroup is all infants (<1 year

old; 11% of the aPAD). For the chronic assessment, the most highly exposed population subgroup is children 1-2 years old (6.7% of the cPAD). The use of anticipated residues (ARs), empirical processing factors, and crop treated information would refine further HED's exposure and risk estimates; however, refinement is not needed at this time. A cancer dietary risk assessment was not performed because dicamba is not a carcinogen.

Drinking Water

Dicamba could potentially be found in drinking water. Environmental fate studies show that the major environmental degradate would be DCSA. DCSA and 5-OH- dicamba are major metabolites, and in the case of DCSA, a major degradate that could potentially be found in drinking water. Sufficient drinking water monitoring data from surface water sources were not available so estimated drinking water concentrations (EDWCs) were determined for surface water resources using PRZM-EXAMS (Pesticide Root Zone Model-Exposure Analysis Modeling System) from application to sugarcane, which has the highest use rate. Surface drinking water estimates (dicamba and DCSA) were included in the dietary exposure assessment. For the purposes of the dietary exposure assessment, the highest (*i.e.*, most conservative) values were used for the acute (367 ppb; parent + DCSA) and chronic (13.75 ppb; parent + DCSA) assessments.

Residential Exposure

Exposure to dicamba may occur in residential settings from treatment of turf around the home and at golf courses. Risks to individuals were assessed in the RED (D317720, 9/13/2005) and are summarized (Section 5.0 of this document). Residential handler assessments were conducted for homeowners applying dicamba to lawns. All handler MOEs are at least 100 and are, therefore, not of concern to HED. Residential post-application assessments were conducted for adults doing yardwork or playing golf on treated turf, and for children playing or consuming soil or pesticide granules while playing on a treated lawn. Even when exposures occur on the day of treatment, all of the residential exposures are not of concern to HED. Residential exposure estimates were used to calculate aggregate risk for the proposed use on sweet corn.

Aggregate Risk

FQPA requires EPA to aggregate exposures from food, water, and residential settings. Acute, short-term and chronic aggregate risks were assessed. Acute and chronic aggregate risk is made up of dietary exposure only (food and drinking water). Because dicamba is used on home lawns, residential exposure was aggregated with dietary exposure for the short-term aggregate risk assessment. Conservative assumptions were built into the aggregate risk assessments. All aggregate risk estimates are not of concern to HED.

Occupational Exposure

Occupational handler exposure based on the proposed use on sweet corn is not expected to differ significantly from that previously assessed for the existing uses on field corn. Therefore, a separate occupational handler risk assessment was not produced for this action on sweet corn. For details on handler risks, see the Dicamba RED, D317720, 9/13/2005. In the RED, risks for occupational exposures were estimated for pesticide applicators as well as for people who may enter treated fields after application. MOEs were calculated for short/intermediate term dermal and inhalation exposures using standard assumptions and unit exposure data for a range of

application methods and equipment. The unit exposure data were taken from the Pesticide Handlers Exposure Database (PHED) and the Outdoor Residential Exposure Task Force (ORETF) studies for professional lawn care operators. All mixer/loader, applicator and mixer/loader/applicator MOEs exceed the target of 100 with a single layer personal-protective equipment (PPE) and, therefore, risks are not of concern to HED.

For the current proposal for use on sweet corn, post-application risk was assessed because it is more common for workers to perform post-application activities (such as detasseling and hand harvesting) in sweet corn fields, compared to the minimal post-application activities typically performed in field corn. Risk for sweet corn detasseling and hand harvesting result in an MOE of 130 on the day of application, which is not of concern to HED. All other post-application MOEs are above the target MOE of 100.

Restricted-Entry Level (REI)

The Distinct® label (EPA Reg. No. 7969-150) lists an REI of 12 hours. Dicamba is listed as Acute Toxicity Category II for Primary Eye Irritation and Primary Skin Irritation. The interim WPS REI for compounds exhibiting Toxicity Category II effects for primary eye and skin irritation is 24 hours (40 CFR Part 156 § 156.208 (c) (1) and (2). **HED requests confirmation of the basis for a 12-hour REI for this product, and recommends that dicamba labels reflect the appropriate REI.**

Recommendations

Provided that the petitioner submits a revised Section F and the appropriate REI is clarified and stated on labels, HED concludes there are no residue chemistry or toxicology data requirements that would preclude the establishment of a conditional registration for the use of dicamba on sweet corn and the following permanent tolerances for combined residues of dicamba and its 5-OH metabolite in/on:

Corn, sweet, forage	0.50 ppm
Corn, sweet, kernel plus cob with husks removed	0.04 ppm
Corn, sweet, stover	0.50 ppm

Conversion of the conditional registration to an unconditional registration may be considered upon submission of additional field residue trials.

2.0 Ingredient Profile

2.1 Summary of Registered/Proposed Uses

Dicamba (2-methoxy-3,6-dichlorobenzoic acid) is a selective benzoic acid herbicide registered for the control of certain broadleaf weeds and woody plants before their emergence. It is an auxin agonist that is readily translocated symplastically and apoplastically with accumulation in meristemic regions of the plant. Sensitive plants exhibit rapid uncontrolled growth characterized by twisting and curling of stems and petioles, stem elongation and swelling and leaf cupping. Weed control is generally achieved in 5 to 7 days.

Registered Uses
Different forms of dicamba (acid and salt) have registered uses on rights of way areas, asparagus, barley, corn (field and pop), grasses grown in pasture and rangeland, oats, proso millet, rye, sorghum, soybeans, sugarcane, and wheat. Application rates range from 0.5 to 2.8 lb ae/A. Residential uses include broadcast and spot treatment on golf courses and lawns.

There were approximately 434 active dicamba products formulated from 6 different forms. Most products are made of the acid, dimethylamine and sodium salt ester forms. The products are formulated as liquids, standard granules and water dispersible granules. The residential products are typically formulated as granular weed and feed formulations or as liquids in concentrates or ready to use sprays.

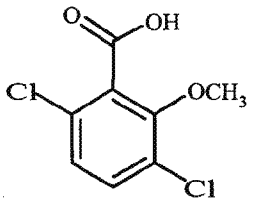
Proposed Uses
Distinct® Herbicide (EPA Reg. No. 7969-150), a multiple active ingredient water-dispersible granule (WDG) formulation containing 21.4% diflufenzopyr and 55% dicamba, has selective postemergence activity. The maximum application rate for sweet corn is 0.125 lbs. ae/A and a maximum of 2 applications are permitted per season. The maximum seasonal use rate is 0.25 lbs. ae/A with a minimum retreatment interval (RTI) of 2 weeks. Surfactants (0.25% v/v) should be added to the postemergence finished spray. The spray volume is 3-50 gal/A by ground equipment. The preharvest interval (PHI) is 32 days for fresh corn and 72 days for stover.

The rotational crop restrictions listed on the label are 7 days for corn and 120 days for all other crops.

The petitioner has proposed an adequate set of directions for use of Distinct® on sweet corn.

2.2 Structure and Nomenclature

Table 2.2. Dicamba Nomenclature

PC Code 029801	
Chemical structure	
Common name	Dicamba acid
Molecular Formula	$C_8H_6Cl_2O_3$
Molecular Weight	221.04
IUPAC name	3,6-dichloro-*o*-anisic acid
CAS name	3,6-dichloro-2-methoxybenzoic acid or 2-methoxy-3,6-dichlorobenzoic acid
CAS #	1918-00-9

Chemical structures of dicamba salts can be found in Attachment 2.

2.3 Physical and Chemical Properties

Table 2.3. Physicochemical Properties of Dicamba.

Parameter	Value		Reference
Dicamba acid (PC Code 029801)			
Melting point	114-116℃ (PAI) 90-100℃ (87% TGAI)		SRR Reregistration Standard, 6/30/89
pH	2.5-3.0 (87% TGAI)		
Density, bulk density, or specific gravity	1.57 g/mL at 25℃ (87% TGAI)		
Water solubility	0.5 g/100 mL at 25℃ (PAI)		
Solvent solubility	dioxane	118.0	
	ethanol	92.2	
	isopropyl alcohol	76.0	
	methylene chloride	26.0	
	acetone	17.0	
	toluene	13.0	
	xylene	7.8	
	heavy aromatic naphthalene	5.2	
Vapor pressure	3.4×10^{-5} mm Hg at 25℃ (PAI)		
Dissociation constant, pK_a	1.97 (PAI)		
Octanol/water partition coefficient	0.1 (PAI)		
UV/visible absorption spectrum	neutral: 511 (275 nm) acidic (pH 0-1): 1053 (281 nm) basic (pH 13-14): 469 (274 nm)		RD D266167, 6/26/00, B. Kitchens

3.0 Hazard Characterization and Dose-Response Assessment

Dicamba has a low acute toxicity via oral, dermal or inhalation route (Acute Toxicity Categories 3 or 4). It is an eye and dermal irritant but it is not a skin sensitizer. Dogs are generally considered to be toxicologically more sensitive when exposed to dicamba. Consistent neurotoxic signs (e.g., ataxia, decreased motor activity, impaired righting reflex and gait) were observed in many studies in rats and rabbits at high doses. There is an increased incidence of abortion in the rabbit developmental toxicity study at doses that also showed maternal toxicity. In a two-generation reproductive toxicity study, offspring toxicity was manifested as decreases in pup weight in all generations at a dose lower than the parental systemic toxicity NOAEL. Developmental studies in rats and rabbits showed no evidence (qualitative or quantitative) for increased susceptibility following *in utero* exposure of dicamba. Dicamba is classified as "not likely to be carcinogenic to humans" by the oral route. Mutagenicity studies did not demonstrate evidence of mutagenic potential for dicamba although some positive results were reported in

published literature. Following oral administration, dicamba is rapidly absorbed and excreted in urine and feces without significant metabolism.

An acute neurotoxicity study in rats was selected for the general population, including infants and children, for an endpoint of concern for a single oral exposure risk assessment. For the short- and intermediate-term incidental oral exposure and the chronic RfD, a multi-generation reproductive toxicity study in rats was selected based on impaired pup growth (decreased pup weights).

The dose and endpoint selected for dermal and inhalation risk assessment for all durations was based on a multi-generation reproductive toxicity study in rats. The multi-generation reproductive toxicity study with a longer duration and a NOAEL of 45 mg/kg/day is protective and appropriate for short-, intermediate- and long-term dermal risk assessments. The 28-day dermal toxicity study in rats was not selected for dermal risk assessment because the offspring effect in the reproductive toxicity study was not measured in this study. In addition, the NOAEL (1000 mg/kg/day) in the 28-day dermal toxicity study would not be protective of the reproductive-offspring effects in the rat multi-generation reproductive toxicity study with a NOAEL of 45 mg/kg/day using a dermal-absorption factor of 15%. Since an oral NOAEL was selected, a 15% dermal-absorption factor was used for route-to-route extrapolation for assessing dermal risk.

The UFs used in determining the acute and chronic RfD exposure limit were 100x (10x for intraspecies variation and 10x for interspecies extrapolation). An additional 3x was applied to acute dietary risk assessment for general population for using a LOAEL instead of a NOAEL. The 3X is considered adequate because a comparison with the rat developmental toxicity study that had similar clinical signs with a NOAEL of 160 mg/kg/day after 10 days of treatment indicates that the NOAEL for the acute neurotoxicity study is unlikely to be more than 3-fold lower than the LOAEL (ACN LOAEL/3 = 100 mg/kg; rat developmental study NOAEL = 160 mg/kg). Therefore, it was determined that an uncertainty factor of 3 for extrapolation of LOAEL to NOAEL was adequate (TXR No. 0050280).

The acute toxicity profile for dicamba is presented in Table 3.0.

Table 3.0. Acute Toxicity of Dicamba

OPPTS Guideline	Study Type	MRID	Results	Toxicity Category
870.1100	Acute oral toxicity / rat	00078444	LD_{50} = > 2740 mg/kg	III
870.1200	Acute dermal toxicity / rat	00241584	LD_{50} = > 2000 mg/kg	III
870.1300	Acute inhalation toxicity / rat	00263861	LC_{50} = > 5.3 mg/L	IV
870.2400	Primary eye irritation / rabbit	00241584	Irritant	II
870.2500	Primary dermal irritation / rabbit	00237955	Irritant	II
870.2600	Dermal sensitization / guinea pig	00263861	Non-Sensitizer	--

3.1 Mode of Action, Metabolism, Toxicokinetic Data

Multiple studies describing the metabolism or the pharmacokinetic of dicamba in rats have been submitted to the Agency. The metabolism study in rats showed that following oral administration, dicamba is rapidly absorbed and excreted. Over 95% is excreted in the urine and the compound is not metabolized or accumulated by the tissues.

The plasma pharmacokinetic studies in rats showed that absorption of radiolabeled dicamba was rapid, with peak plasma concentrations found within 2 hours of treatment. Absorption was not saturated, even at the highest dose, as indicated by increasing plasma concentrations with doses. However, the increase in plasma concentration was non-linear and disproportionate from one dose to the next doses, which is consistent with saturation of excretion. No significant treatment-related differences between the sexes or time of radiolabel administration were found. Another plasma pharmacokinetic study suggested that dicamba acts as an inhibitor of renal anion transport.

3.2 FQPA

Summary

The database is adequate in terms of endpoint studies and dose response information to select appropriate endpoints for prenatal or postnatal risk for infants and children. There is no evidence (qualitative or quantitative) of increased susceptibility following *in utero* exposure in the developmental toxicity studies in rats and rabbits. There was evidence of increased sensitivity to the offspring following pre- / postnatal exposure in the two-generation reproductive toxicity study in rats. In that study, offspring toxicity was manifested as decreased pup body weight in all generations at a dose lower than the parental systemic toxicity NOAEL. However, the degree

of concern is low for the quantitative susceptibility because the risk assessment was based on the very same effect seen in the pups with a definitive NOAEL. There are no concerns or residual uncertainties for pre- and postnatal toxicity.

After considering the available toxicity data, the risk assessment team determined that a DNT is not required based on the following reasons: (1) although clinical signs of neurotoxicity were seen in pregnant animals, no evidence of developmental anomalies of the fetal nervous system were observed in the prenatal developmental toxicity studies, in either rats or rabbits, at maternally toxic doses up to 300 or 400 mg/kg/day, respectively; (2) there were no evidence of behavioral or neurological effects on the offspring in the two-generation reproductive toxicity study in rats; (3) the ventricular dilation of the brain in the combined chronic toxicity and carcinogenicity study in rats was only observed in females at the high dose after two years exposure. The significance of this observation is questionable since no similar histopathological finding was seen in the subchronic neurotoxicity study. In addition, the dicamba risk assessment team evaluated the quality of the exposure data; and, based on these data, recommended that the FQPA SF be reduced to 3x for acute dietary risk assessment for the use of a LOAEL instead of a NOAEL and 1x for all other risk assessments.

3.2.1 Adequacy of the Toxicity Data Base

The following studies are available in the toxicity database:

- Developmental toxicity studies in rats and rabbits (acceptable).
- Two-generation reproductive toxicity study in rats (acceptable).
- Acute and subchronic neurotoxicity studies in rats (acceptable).

The toxicity profile for dicamba is presented in Attachment 1 to this memorandum.

3.2.2 Evidence of Neurotoxicity

There is evidence of neurotoxicity resulting from exposure to dicamba. In the acute neurotoxicity study, clinical signs of neurotoxicity consisted of impaired gait and righting reflex, decreased arousal and rears/minutes, and rigidity upon handling were observed at 300 mg/kg bw or above. At higher dose levels, the effects were more pronounced with additional effects. The subchronic neurotoxicity study in rats showed rigid body tone, impaired righting reflex and gait at 768 mg/kg.

In the developmental toxicity studies in rats, ataxia, stiffening of the body when touched, and decreased motor activity were seen at 400 mg/kg in the dams. The developmental toxicity study in rabbits showed that at 150 mg/kg the dams presented signs of ataxia, rales and decreased motor activity.

A two-generation reproductive toxicity study demonstrated tense/stiff body tone and slow righting reflex in the dams from both generations at the 450 mg/kg dose level. It should be noted that the signs of neurotoxicity were consistent across several studies.

3.2.3 Developmental Toxicity Studies

In a developmental toxicity study (MRID No. 00084024), pregnant (CD Charles River) rats (25/dose group) received gavage administration of dicamba (85.3%) in corn oil at dose levels of 0, 64, 160, or 400 mg/kg/day during gestation days 6 through 19. Maternal toxicity limited to the high dose (400 mg/kg/day) was characterized by mortality in three gravid dams and one non-gravid dam that exhibited neurotoxic signs prior to death; clinical signs of nervous system toxicity that included ataxia, salivation, stiffening of the body when held, and decreased motor activity; statistically significant ($p<0.05$) decreases in body weight gain during the dosing period; and concomitant decreases in food consumption. Dicamba had no effect on any of the cesarean parameters. For maternal toxicity, the NOAEL was 160 mg/kg/day and the LOAEL was 400 mg/kg/day based on mortality, clinical signs, body weight changes and decreases in food consumption. No treatment-related fetal gross external, skeletal or visceral anomalies (malformations or variations) were seen at any dose level. For developmental toxicity, the NOAEL was >400 mg/kg/day; a LOAEL was not established. This study is classified **acceptable/guideline** (OPPTS 870.3700a) and satisfies the requirements for a developmental toxicity study in the rat.

In a developmental toxicity study (MRID No. 42429401), inseminated New Zealand White (NZW) rabbits (19-20/dose) were given oral capsules containing dicamba (90.5%) at dose levels of 0, 30, 150, or 300 mg/kg/day from days 6 through 18 of gestation. No maternal or developmental toxicity was observed at 30 mg/kg/day. At 150 mg/kg/day, maternal toxicity was characterized by abortion (5%) and clinical signs such as ataxia, rales, decreased motor activity. At 300 mg/kg/day maternal toxicity was manifested by abortions (20%), clinical signs, decreased body weight and body weight gain and food consumption. Developmental toxicity at 300 mg/kg/day was manifested by irregular ossification of the nasal bones of the skull. At 150 mg/kg/day, increased incidence of abortion was observed and was considered developmental toxicity. In a range-finding study, NZW rabbits were dosed at 0, 62.5, 125, 250, or 500 mg/kg/day from days 6 through 18 of gestation. No maternal or developmental toxicity was observed at 62.5 mg/kg/day. Treatment-related maternal toxicity was manifested by mortality, increased resorptions and reduction in the litter size at 500 mg/kg/day. Clinical signs occurred at 125, 250, and 500 mg/kg/day. Cesarean sections revealed no treatment-related differences between treated and control groups, and no external malformation or variations were seen in any of the fetuses of the treated does. Based on the results of these studies, the NOAEL for maternal toxicity was 62.5 mg/kg/day and the LOAEL was 150 mg/kg/day based on increased incidences of abortion and clinical signs (i.e., decreased motor activity, ataxia). For developmental toxicity, the NOAEL was 62.5 mg/kg/day and the LOAEL was 150 mg/kg/day based on increased incidence of abortion. This study is classified **acceptable/guideline** (OPPTS 870.3700b; OECD 414) and satisfies the requirements for a developmental toxicity study in the rabbit.

3.2.4 Reproductive Toxicity Study

In a two-generation reproductive toxicity study (MRID 43137101), Sprague-Dawley rats (32 or 28/group) received dicamba technical (86.5%) in the diet at dose levels of 0, 500, 1500, or 5000 ppm (0, 40, 122, or 419 mg/kg/day for males and 0, 45, 136 or 450 mg/kg/day for females, respectively) for two generations. Systemic toxicity was observed at 5000 ppm, manifested as

clinical signs in dams from both generations during lactation (tense/stiff body tone and slow righting reflex) and significantly increased relative liver to body weights (112% of control) in both generations and sexes, adults as well as weanlings. The increase (107%) in relative kidney weights observed at 1500 and/or 5000 ppm were not considered to be toxicologically significant due to lack of corroborative gross or histopathological lesions in the kidneys. Sexual maturation among male pups in the F1 generation was significantly delayed at 5000 ppm. Similar effects were not seen in females. Significantly decreased pup body weights were observed in all generations and matings at 1500 ppm (86 - 90% of control) and at 5000 ppm (74 - 94% of control) throughout lactation. For parental systemic toxicity, the NOAEL was 122 and 136 mg/kg/day for males and females, respectively, and the LOAEL was 419 and 450 mg/kg/day, in males and females, respectively, based on clinical signs of neurotoxicity. For reproductive toxicity, the NOAEL was 122 mg/kg/day and the LOAEL was 419 mg/kg/day based on delayed sexual maturation in F_1 males. For offspring toxicity, the NOAEL was 45 mg/kg/day and the LOAEL was 136 mg/kg/day based on decreased pup body weight. This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproductive toxicity study in the rat.

3.2.5 Additional Information from Literature Sources

No additional relevant toxicity studies from published literature were identified.

3.2.6 Pre-and/or Postnatal Toxicity

3.2.6.1 Determination of Susceptibility

The pre- and postnatal toxicology database for dicamba includes rat and rabbit developmental toxicity studies and a two-generation reproduction toxicity study in rats. There was no evidence (qualitative or quantitative) of increased susceptibility following *in utero* exposure in the developmental toxicity studies in rats and rabbits. There was evidence of increased sensitivity of the offspring following pre-/postnatal exposure in the two-generation reproduction study in rats. In that study, offspring toxicity was manifested as decreased pup body weight in all generations at a dose lower than the parental systemic toxicity NOAEL. However, there is low concern and there are no residual uncertainties for the increased susceptibility for the following reasons. The NOAEL of 45 mg/kg/day identified in this study was chosen for risk assessments for all routes and exposure durations other than acute oral exposures. Since this NOAEL is the lowest (most sensitive endpoint) in the dicamba toxicity data base, and the dose response observed in the study is well defined, assuring that this dose is a clear NOAEL, use of the NOAEL and endpoint for risk assessment is protective for all observed toxic effects of the chemical. The endpoint (decreased pup body weight) is not expected to occur as a result of a single (acute) exposure and was, therefore, not deemed appropriate for assessing acute oral exposures.

3.2.6.2 Degree of Concern Analysis and Residual Uncertainties

The degree of concern is low for the quantitative susceptibility seen in the 2-generation reproduction study in rats because the risk assessment was based on the most sensitive endpoint

with a definitive NOAEL. There are no concerns or residual uncertainties for pre- and postnatal toxicity.

3.2.7 Recommendation for a Developmental Neurotoxicity Study

After considering the available toxicity data, the risk assessment team determined that a DNT is not required based on the following reasons: (1) although clinical signs of neurotoxicity were seen in pregnant animals at high doses, no evidence of developmental anomalies of the fetal nervous system were observed in the prenatal developmental toxicity studies, in either rats or rabbits, at maternally toxic doses up to 300 or 400 mg/kg/day, respectively; (2) there were no evidence of behavioral or neurological effects on the offspring in the two-generation reproductive toxicity study in rats; (3) the ventricular dilation of the brain in the chronic toxicity study was only observed in females at the high dose after two years exposure. The significance of this observation is questionable since no similar histopathological finding was seen in the subchronic neurotoxicity study.

3.2.8 FQPA Safety Factor for Infants and Children

EPA has determined that reliable data show that it would be safe for infants and children to reduce the FQPA safety factor to 3X for acute oral exposures and to 1X for all other routes and durations of exposure. That decision is based on the following findings:

i. The toxicity database for dicamba is complete.

ii. Consistent neurotoxic signs (e.g., ataxia, decreased motor activity, impaired righting reflex and gait) were observed in many studies in rats and rabbits at high doses. After considering the available toxicity data, EPA determined that there is no need for a developmental neurotoxicity study or additional UFs to account for neurotoxicity for the following reasons: (1) although clinical signs of neurotoxicity were seen in pregnant animals, no evidence of developmental anomalies of the fetal nervous system were observed in the prenatal developmental toxicity studies, in either rats or rabbits, at maternally toxic doses up to 300 or 400 mg/kg/day, respectively; (2) there was no evidence of behavioral or neurological effects on the offspring in the two-generation reproduction study in rats; (3) the ventricular dilation of the brain in the combined chronic toxicity and carcinogenicity study in rats was only observed in females at the high dose after two years' exposure. The significance of this observation is questionable, since no similar histopathological finding was seen in the subchronic neurotoxicity study.

iii. There is no evidence that dicamba results in increased susceptibility in *in utero* rats or rabbits in the prenatal developmental toxicity studies. Although there is quantitative evidence of increased susceptibility in the two-generation reproduction study in rats, the degree of concern is low because there is a well established offspring toxicity NOAEL in the study and the risk assessment team did not identify any residual uncertainties after establishing toxicity endpoints and traditional UFs to be used in the risk assessment of dicamba for all routes and durations of exposure, except acute oral exposures.

iv. EPA selected an endpoint from the acute neurotoxicity study in rats for use in assessing acute oral exposures. In this study, neurotoxicity was seen in both sexes at the lowest dose tested, 300 mg/kg/day. Since a NOAEL was not established in the study, EPA has determined that an FQPA safety factor of 3X must be used in acute oral risk assessments for dicamba to account for uncertainty arising from the use of LOAEL instead of NOAEL. EPA has reduced the factor from 10X to 3X based on the following considerations. A comparison of the acute neurotoxicity (ACN) study with the rat developmental toxicity study that showed similar clinical signs and a NOAEL of 160 mg/kg/day after 10 days of treatment indicates that the NOAEL for the acute neurotoxicity study is unlikely to be more than 3- fold lower than the LOAEL (ACN LOAEL/3 = 100 mg/kg; rat developmental study NOAEL = 160 mg/kg). Therefore, it was determined that an uncertainty factor of 3X for extrapolation of LOAEL to NOAEL was adequate.

v. There are no residual uncertainties identified in the exposure databases. The dietary food exposure assessments were performed based on 100%CT and tolerance-level residues. Conservative ground and surface water modeling estimates were used. Similarly, conservative Residential SOPs were used to assess post-application exposure of children as well as incidental oral exposure of toddlers. These assessments will not underestimate the exposure and risks posed by dicamba.

3.3 Classification of Carcinogenic Potential

In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), dicamba is classified as not likely to be carcinogenic to humans. This was based on negative cancer studies in rats and mice which were tested at adequate dose levels to assess the carcinogenicity of dicamba (TXR No. 0053647).

3.4 Summary of Toxicological Doses and Endpoints for Use in Human Risk Assessments

Levels of concern for dicamba risk assessments are presented in Table 3.4.1. Endpoints and doses selected for risk assessment are shown below in Table 3.4.2.

Table 3.4.1 Summary of Levels of Concern for Risk Assessment

Route	Duration			
	Acute (1 day)	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Occupational (Worker) Exposure				
Dermal	NA	100	100	100
Inhalation	NA	100	100	100
Residential (Non-Dietary) Exposure				
Oral	300	100	100	N/A

Dermal	300	100	100	100
Inhalation	300	100	100	100

Table 3.4.2. Summary of Toxicology Endpoint Selection for Dicamba

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General population including infants and children	LOAEL = 300 mg/kg/day UF = 300 Acute RfD = 1 mg/kg/day	FQPA SF = 1X aPAD = acute RfD / FQPA SF = 1.0 mg/kg/day	Acute Neurotoxicity Study in Rats LOAEL = 300 mg/kg/day (LDT) based on clinical signs of neurotoxicity.
Chronic Dietary (All populations)	NOAEL= 45 mg/kg/day UF = 100 Chronic RfD = 0.45 mg/kg/day	FQPA SF = 1X cPAD = chronic RfD / FQPA SF = 0.45 mg/kg/day	Multi-generation reproductive toxicity study in rats LOAEL=136 mg/kg/day based on impaired pup growth (decreased pup weights).
Short- (1 - 30 Days) and Intermediate- (1-6 months) Term Incidental Oral	Oral NOAEL= 45 mg/kg/day	Residential LOC for MOE = 100	Multi-generation reproductive toxicity study in rats See above, under chronic dietary.
Short-, Intermediate- and Long- (>6 months) Term Dermal	Oral NOAEL= 45 mg/kg/day (Dermal-absorption rate = 15%)	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	Multi-generation reproductive toxicity study in rats See above, under chronic dietary.
Short-, Intermediate- and Long-Term Inhalation	Oral NOAEL= 45 mg/kg/day (Inhalation absorption rate= 100%)	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	Multi-generation reproductive toxicity study in rats See above, under chronic dietary.
Cancer (Oral, dermal, inhalation)	Dicamba is classified as not likely to be carcinogenic to humans.		

3.5 Recommendation for Aggregate Exposure Risk Assessments

A common toxicological endpoint (decreased pup growth) of concern was identified for short-, intermediate- and long-term durations via the oral, dermal (oral equivalent) and inhalation (oral equivalent) routes. Therefore, the aggregate exposure risk assessment should include exposure across the oral, dermal and inhalation routes as appropriate for the populations of concern.

3.6 Endocrine Disruption

EPA is required under the Federal Food, Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate. Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program.

4.0 Dietary Exposure/Risk Characterization

4.1 Pesticide Metabolites and Degradates of Concern

A summary of dicamba metabolites and environmental degradates to be included in the dietary risk assessment and tolerance expression may be found in Table 4.1. DCSA and 5-OH- dicamba are major metabolites, and in the case of DCSA, a major degradate that could potentially be found in drinking water. Specific toxicity data are not available for either of these compounds. Based on their structural similarity to the parent, the risk assessment team has concluded that they may have similar toxicity as the parent, and should be included in the dietary risk assessment.

Table 4.1 Summary of Dicamba Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression [1]

	Matrix	Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop - Most grains	Dicamba and 5-OH Dicamba	Dicamba and 5-OH Dicamba
	Primary Crop – Asparagus	Dicamba and DCSA	Dicamba and DCSA
	Primary Crop - Soybean and Aspirated Grain Fractions	Dicamba, DCSA, and 5-OH Dicamba	Dicamba, DCSA, and 5-OH Dicamba
	Rotational Crop	Not Required [2]	Not Required [2]
Livestock	Ruminant	Dicamba and DCSA	Dicamba and DCSA
	Poultry	Not Required	Not Required
Drinking Water		Dicamba and DCSA	Not Applicable

[1] Nomenclature of metabolites/degradates: 3,6-dichloro-5-hydroxybenzoic acid = 5-OH; 3,6-dichloro-2-hydroxybenzoic acid = 3,6-dichlorosalicylic acid = DCSA;

[2] Tolerances and dietary risk assessment are not required provided the registrants specify a 120-day plant-back interval (PBI).

4.2 Environmental Fate

Reference: Memo, Ibrahim Abdel-Saheb, D317705, 5/31/2005.

Aerobic soil metabolism is the main degradative process for dicamba. A single observed half-life for dicamba was six days; with formation of the intermediate non-persistent degradate DCSA. DCSA degraded at roughly the same rate as dicamba; the final metabolites were carbon dioxide and microbial biomass. Dicamba is stable to abiotic hydrolysis at all pH's and photodegrades slowly in water and on soil. Dicamba is more persistent under anaerobic soil:water systems in the laboratory, with a half-life of 141 days. The major degradate under anaerobic conditions was DCSA, which was persistent, comprising > 60% of the applied after 365 days of anaerobic incubation. No other anaerobic degradates were present at > 10% during the incubation. There are no acceptable data for the aerobic aquatic metabolism of dicamba; supplemental information indicates that dicamba degrades more rapidly in aquatic systems when sediment is present.

Dicamba is very soluble (6100 ppm) and very mobile (K_{oc} = 13.4) in the laboratory. Because dicamba is not persistent under aerobic conditions, very little dicamba could be expected to leach to groundwater. If any dicamba did reach anaerobic ground water, it would be somewhat persistent (due to its anaerobic half-life of 141 days); any DCSA that reached ground water would be expected to persist. Results from two acceptable field dissipation studies conducted with dimethylamine salt of dicamba, indicated that dicamba dissipated with a half-life range of 4.4 to 19.8 days. The DCSA was the major degradate in both studies. Both, dicamba and its degradate (DCSA) were found in soil segments deeper than 10 cm.

Dicamba is not expected to bioaccumulate in aquatic organisms because it is an anion at environmental pHs (pKa = 1.9).

4.3 Drinking Water Residue Profile

The most recent drinking water assessment was performed for the RED in 2005 (see reference above). EFED has stated that the sugarcane use results in the highest drinking water exposure potential. Therefore, the drinking water estimates for sugarcane from the RED were used to estimate dietary exposure to dicamba from food and drinking water sources.

The Tier II screening models PRZM and EXAMS with the Index Reservoir and Percent Crop Area adjustment (IR-PCA PRZM/EXAMS) were used to determine estimated surface water concentrations of dicamba and its degradate DCSA. The combined values for parent dicamba and DCSA are 367 ppb (or 0.367 ppm; acute) and 13.75 ppb (or 0.1375 ppm; chronic).

Results from the SCI-GROW screening model predict that the maximum chronic and acute concentration of parent dicamba acid, and its degradate DCSA in shallow ground water is not expected to exceed 0.016 µg/L, and 0.0081µg/L, respectively, for the current maximum seasonal use rate on sugarcane. Surface water concentrations are shown below in Table 4.3.

Table 4.3. Drinking Water Estimates for Dicamba and DCSA

Crop (application method)	Model EDWCs (µg/L)					
	Dicamba			DCSA		
	Acute	One-in-10-year annual mean	36 year overall mean	Acute	One-in-10-year annual mean	36 year overall mean
Surface Water						
FL-Sugarcane (Ground)	**357**	**13**	5.23	**10.1**	**0.75**	0.4
FL-Sugarcane (Aerial)	346	12.9	5.38	10.9	0.813	0.47
LA-Sugarcane (Ground)	233	9.74	3.13	8.79	0.66	0.32
LA-Sugarcane (Aerial)	230	9.74	3.44	9.74	0.73	0.39
Note that these estimates assume one application @ 2.8 lb ai/A (parent); and 0.446 lb ai/A (DCSA) and a crop area factor of 0.87						

4.4 Food Residue Profile

Background

Interregional Research Project No. 4 (IR-4) has submitted a petition on behalf of the Agricultural Experiment Stations of MN, ND and WI proposing the following permanent tolerances for the combined residues of the herbicide dicamba and its 5-OH metabolite in/on the following raw agricultural commodities (RACs):

Proposed Tolerances

Corn, sweet, forage	1.0 ppm
Corn, sweet, fresh	0.1 ppm
Corn, sweet, stover	1.0 ppm

Tolerances for residues of dicamba and its 5-OH metabolite have been established for corn grain, corn forage, corn fodder, wheat grain, wheat straw, barley grain, and barley straw at 0.5 ppm; and for field corn forage, field corn stover and popcorn stover at 3.0 ppm (40 CFR § 180.227(a)). Tolerances for dicamba and its 2-OH metabolite (DCSA) have been established at 0.05 ppm for soybeans; 0.1 ppm for soybean hay and soybean forage; and on cattle, goats, hogs, horses, and sheep meat, fat, and meat byproducts at 0.2 ppm, liver and kidney at 1.5 ppm, and milk at 0.3 ppm (40 CFR §180.227(b)).

Nature of the Residue

Plants: The nature of the residue in plants is adequately understood (F. Griffith, 02-MAY-1996, PP#6F4604, D220469). The residues to be regulated in barley, corn, cotton, oats, wheat, and grasses are dicamba and its 5-OH metabolite; in asparagus the residues to be regulated are dicamba and DCSA; and in soybeans and aspirated grain fractions, the residues to be regulated are dicamba, 5-OH dicamba and DCSA.

Livestock: The nature of the residue in ruminants and poultry is adequately understood (L. Cheng, 07-MAR-1996, D204482). The residues to be regulated in livestock are dicamba and its DCSA metabolite.

Residue Analytical Methods

The petitioner has presented an adequately validated capillary GC methods with electron capture detection (GC/ECD) residue analytical method to determine the magnitude of dicamba and 5-OH dicamba residues in plant commodities (barley, corn, cotton, cotton processed fractions, pasture grass, peanut, sorghum, soybean, sugar cane, tomato, tomato processed fractions, wheat and wheat processed fractions). Pesticide Analytical Manual (PAM) Volume II lists Method I and II, GC/ECD, for the enforcement of tolerances on dicamba and its metabolite 5-OH dicamba in/on plant commodities and milk.

Multiresidue Method

Documentation from the FDA, PAM Volume I, Appendix II and Table 201-D, shows that dicamba is partially recovered (71 - 76%) using Protocol B.

Crop Field Trials

A total of 9 field residue trials were conducted in Regions 1 (1 trial), 2 (1 trial), 3 (1 trial), 5 (3 trials), 6 (1 trial), 10 (1 trial) and 12 (1 trial). The number and location do not match that suggested in Table 5 of OPPTS Test Guidelines Series 860.1500 for sweet corn: 12 trials conducted in Regions 1 (2 trials), 2 (1 trial), 3 (1 trial), 5 (5 trials), 10 (1 trial), 11 (1 trial) and 12 (1 trial). The petitioner previously submitted the results of 20 field corn residue trials. HED can generally translate field corn forage and stover data to sweet corn. However, in this case, translation is not appropriate as the application rate in the field corn trials was >10X the maximum proposed sweet corn application rate.

HED requests that the petitioner submit an additional 3 sweet corn residue trials conducted in Regions 1 (1 trial), 5 (1 trial) and 11 (1 trial). Permanent tolerances and a conditional registration may be established while these trials are conducted. Based on the available data, the following tolerance for residues of the herbicide dicamba and its 5-OH metabolite are appropriate for this petition:

Recommended Tolerances

Corn, sweet, forage	0.50 ppm
Corn, sweet, kernel plus cob with husks	0.04 ppm
Corn, sweet, stover	0.50 ppm

A revised Section F is required.

Processed Food/Feed

As there are no processed commodities associated with sweet corn, processing studies are not required to support the subject petition.

Meat, Milk, Poultry, Eggs (MMPE)

Given that there are already dicamba tolerances established on major livestock feed items at high levels (i.e., aspirated grain fractions at 5100 ppm, grass forage at 125 ppm and wheat forage at 20 ppm), HED concludes that the dietary burden to livestock will not be affected by the use of dicamba on sweet corn. Therefore, the existing MMPE tolerances have not been reassessed.

Confined and Field Accumulation in Rotational Crops

Based on the results of a confined rotational crop study (memo S. Chun & W. Donovan, 25-JUN-1998; D228694), HED has concluded that the plantback intervals specified on the Distinct® label (7 days for corn and 120 days for all other crops) are appropriate.

4.5 International Residue Limits

There is neither a Codex proposal, nor Canadian or Mexican limits for residues of dicamba in/on sweet corn. Therefore, a compatibility issue is not relevant to the proposed tolerance.

4.6 Dietary Exposure and Risk

Memo, S. Levy, D347355.

Dicamba acute and chronic dietary exposure assessments were conducted using the DEEM FCID™, Version 2.03 which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. The 1994-96, 98 data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods "as consumed" (e.g., apple pie) are linked to EPA-defined food commodities (e.g., apples, peeled fruit - cooked; fresh or N/S; baked; or wheat flour - cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA/ARS and EPA. For chronic exposure assessment, consumption data are averaged for the entire U.S. population and within population subgroups. Based on analysis of the 1994-96, 98 CSFII consumption data, which took into account dietary patterns and survey respondents, HED concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50+ years old.

For chronic dietary exposure assessment, an estimate of the residue level in each food or food-form (e.g., orange or orange juice) on the food commodity residue list is multiplied by the average daily consumption estimate for that food/food form to produce a residue intake estimate. The resulting residue intake estimate for each food/food form is summed with the residue intake estimates for all other food/food forms on the commodity residue list to arrive at the total average estimated exposure. Exposure is expressed in mg/kg body weight/day and as a percent of the cPAD. This procedure is performed for each population subgroup. A cancer dietary

assessment was not conducted because dicamba was classified as not likely to be carcinogenic to humans.

The acute and chronic dietary exposure assessments were conducted using tolerance-level residues, DEEM default processing factors and 100% CT information for all registered and proposed use sites. Drinking water values were incorporated directly into the acute and chronic dietary assessments.

Table 4.6. Summary of Dietary Exposure and Risk for Dicamba.

Population Subgroup	Acute Dietary[1] (95th Percentile)		Chronic Dietary[1]	
	Dietary Exposure (mg/kg/day)	%aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*
U.S. Population (total)	0.044066	4.4	0.012091	2.7
All Infants (< 1 year old)	0.109311	**11**	0.020233	4.5
Children 1-2 years old	0.076605	7.6	0.030196	**6.7**
Children 3-5 years old	0.068164	6.8	0.027604	6.1
Children 6-12 years old	0.048314	4.8	0.018991	4.2
Youth 13-19 years old	0.032048	3.2	0.011752	2.6
Adults 20-49 years old	0.034236	3.4	0.009961	2.2
Adults 50+ years old	0.026832	2.7	0.007616	1.7
Females 13-49 years old	0.031439	3.1	0.008935	2.0

[1] Acute dietary endpoint of 1.0 mg/kg/day applies to the general U.S. population and all population subgroups. Chronic dietary endpoint of 0.45 mg/kg/day applies to the general U.S. population and all population subgroups.
* The highest %aPAD and %cPAD are bolded.

4.6.1 Acute Dietary Exposure/Risk

For the acute assessment, the most highly exposed population subgroup is all infants (<1 year old; 11% of the aPAD). The acute assessment concludes that the acute dietary exposure estimates is not of concern to HED for the general U.S. population or any population subgroup. The use of ARs, empirical processing factors, and %CT data would refine further HED's exposure and risk estimates; however, refinement is not needed at this time.

4.6.2 Chronic Dietary Exposure/Risk

For the chronic assessment, the most highly exposed population subgroup is children 1-2 years old (6.7% of the cPAD). The chronic assessments conclude that chronic dietary exposure estimates are not of concern to HED for the general U.S. population or any population subgroup. The use of ARs, empirical processing factors, and %CT data would refine further HED's exposure and risk estimates; however, refinement is not needed at this time.

4.6.3 Cancer Dietary Risk

A cancer dietary-exposure assessment was not conducted because dicamba was classified as not likely to be carcinogenic to humans.

5.0 Residential (Non-Occupational) Exposure/Risk Characterization

Residential uses of dicamba have been previously assessed by HED for the RED (Memo, D317701, T. Dole, 08/26/2005). Conclusions from the last residential risk assessment have been summarized below. Residential exposures were aggregated with dietary exposure in Section 6.0 of this document (episodic ingestion of granules was not aggregated). For details on the assumptions and data used to estimate risks, see the 08/26/2005 memo cited above.

5.1 Residential Handler Exposure and Risk

Dicamba is registered for use on residential sites, including home lawns and golf courses. Residential dicamba products are typically formulated as dry weed and feed products, as liquid concentrates or as ready-to-use sprays. Spot and broadcast treatments are both included on dicamba labels. Exposures are expected to be short-term in duration for broadcast treatments because the label allows only two broadcast treatments per year. Exposures are also expected to be short-term in duration for spot treatments because the labels recommend repeat applications in two to three weeks.

In the last risk assessment, seven handler exposure scenarios were assessed for homeowner application to lawns. The scenario with the highest exposure is for residential handlers who mix/load and apply dicamba using a hose-end sprayer (mix your own). Dermal and inhalation exposure is 0.012 mg/kg/day and results in an MOE of 3,800. All residential handler exposure scenarios are not of concern to HED.

5.2 Residential Post-Application Exposure and Risk

Several post-application residential exposure scenarios were assessed for dicamba in the last risk assessment, including toddlers playing on treated turf. The highest three of these are summarized below.

- Short-term exposure for toddlers playing on treated turf
- Short-term exposure for residents doing yardwork on treated turf
- Acute exposure for toddlers from incidental oral ingestion of granules

Details on the post-application risk assessments can be found in the last risk assessment (D317701, 08/26/2005). In summary, for children, incidental oral exposure (hand-to-mouth, object-to-mouth and soil ingestion) was combined with dermal exposure. For adults, risk is based on dermal exposure only (inhalation exposure is expected to be negligible). Estimated risks for all scenarios are not of concern to HED. The results of the residential post-application risk assessment are shown below in Table 5.2.

Table 5.2. Residential Post-Application Risks for Dicamba[1]

Population and Exposure Scenario	Route(s) of Exposure	Exposure (mg/kg/day)	Risk Estimate (MOE)
Short-term Risk			
Toddlers Playing	Dermal, Hand-to-Mouth, Object-to-	0.014	3,200

	Mouth, Soil Ingestion		
Adults Doing Yardwork	Dermal	0.0037	12,000
Episodic Granule Ingestion			
Toddlers	Oral Ingestion	0.2	1,500

1. MOE = NOAEL/exposure; NOAEL = 45 mg/kg/day.

6.0 Aggregate Exposure and Risk Assessment/Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard, or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. Since residential exposure is expected, aggregate exposure consists of exposure from residential, food and drinking water sources.

Acute and chronic aggregate risks were assessed based on dietary exposure from food and drinking water sources. Since there are residential uses, short-term aggregate risks were assessed, but intermediate-term aggregate risks were not considered as residential exposure is not expected to occur for more than 30 days. Cancer aggregate risk was not assessed since dicamba is not a carcinogen.

6.1 Acute Aggregate Risk

It is HED policy not to aggregate acute residential exposures with acute dietary exposures, since it is unlikely that these types of exposures would occur in the same day. Thus, the acute dietary assessment in Section 4.6 represents acute aggregate risk. As stated in Section 4.6, the acute dietary exposure assessment was conducted using tolerance-level residues, DEEM default processing factors and 100% CT information for all registered and proposed use sites. Drinking water values were incorporated directly into the assessment.

The most highly exposed population subgroup is all infants (<1 year old; 11% of the aPAD). These assessments conclude that the acute and chronic dietary exposure estimates are not of concern to HED for the general U.S. population or any population subgroup. The use of ARs, empirical processing factors and percent crop treated data would refine further HED's exposure and risk estimates; however, refinement is not needed at this time. Acute aggregate risk is not of concern to HED for any population.

6.2 Short-term Aggregate Risk

The short term aggregate assessment is comprised of exposure from food, water and residential activities (handler and post-application). Average food and water exposure estimates were used in the assessment. HED conducted a conservative short-term aggregate assessment that assumed adults handle dicamba during lawn treatment as well as become exposed through the diet and post-application activity on a treated lawn. The residential handler scenario that resulted in the highest exposures, mix/load/apply with a (mix your own) hose-end sprayer, was combined with

exposure from the yardwork post-application scenario for the adult assessment, while exposure from the toddler playing on turf scenario was used in the assessment for children.

The results of all of the short-term aggregate assessments are presented in Table 6.2. HED is generally not concerned if the MOEs exceed the target which, for this assessment, is 100. The MOEs for all scenarios are greater than 100 and are not of concern to HED. As stated in the previous section, these are likely to be overestimates and the actual exposures are likely to be much lower.

Table 6.2. Short-Term Aggregate Risk Calculations For Dicamba

Population	Food + Water Exposure mg/kg/day	Incidental Oral Exposure, mg/day	Dermal Dose, mg/kg/day	Combined Exposure, mg/kg/day[1]	MOE Food + Water+ Incidental Oral + Dermal[2]
Adult: Residential Handler and Post-Application[3]	0.012	0	0.016	0.028	1,600
Child: Post-Application (1-2 years old)	0.030	0.0078	0.0062	0.044	1,000

1. Combined exposure includes dermal, inhalation (for handlers only), and dietary exposure.
2. The short-term NOAEL of 45 was used to calculate the MOE (NOAEL/exposure=MOE). The LOC is 100.
3. Dietary exposure from the general adult population subgroup was used as this group had the highest dietary exposure of any adult subgroup.

6.3 Chronic Aggregate Risk

Since the residential uses of dicamba are not expected to occur over the long-term (or chronic) duration, chronic aggregate risk is comprised of dietary exposure only, from food and water sources. The chronic dietary assessment in Section 4.6 represents chronic aggregate risk. As stated in Section 4.6, the chronic dietary exposure assessment was conducted using tolerance-level residues, DEEM default processing factors and 100% CT information for all registered and proposed use sites. Drinking water values were incorporated directly into the assessment.

The most highly exposed population subgroup is children 1-2 years old (6.7% of the cPAD). Chronic aggregate risk is not of concern to HED for any population.

7.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for dicamba and any other substance, and dicamba does not appear to produce a toxic metabolite

produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that dicamba does not have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

8.0 Occupational Exposure/Risk Pathway

Distinct® herbicide is proposed for control of annual and perennial broad leaf weed species in sweet corn. Distinct® is a WDG herbicide that is comprised of 0.20 lb ae diflufenzopyr per pound of product and 0.50 lb ae dicamba per pound of product. The proposed new uses comprise an amendment to the EPA Registered Product No. 7969-150 which is registered for use on field corn and non-crop areas.

For sweet corn, applications may be made from pre-plant to post-emergence when corn is up to 24" tall. For biannual or perennial weeds, make applications when weeds are in the rosette stage before bolting, in the bud stage or in the fall prior to a killing frost.

Table 8. Use Pattern Summary of Proposed New Uses of Distinct® Herbicide on Sweet Corn.

Formulation	Wettable Granule; dicamba 0.50 lb ae/ lb product.
Use Site	Sweet Corn
Application Method	Ground
Maximum Application Rate* pounds ae/A	Sweet corn - 0.25 lb product/A Seasonal max - Sweet corn 0.375 lb product/A
Frequency/Timing	Two applications/season; 14 day RTI
PHI	Sweet corn = 72 days dry grain and stover; 32 days for ears and stover.
REI	Label lists 12 hours, needs clarification- see below.
Manufacturer	BASF Corporation

* Sweet corn max rate = 4 oz product/A = 0.25 lb product/A * 0.50 lb ae/lb product dicamba = 0.125 lb ae/A

Occupational exposure based on the proposed use on sweet corn is not expected to differ significantly from that previously assessed for the existing uses on field corn. Therefore, a

separate occupational risk assessment was not produced for the sweet corn use. Instead, the reader is directed to the last risk assessment (Memo, C. Olinger, D317720, 9/13/2005). A summary of the results of occupational risks is presented below.

Occupational Handler Risk

MOEs for occupational handler exposure were calculated for short/intermediate term dermal and inhalation exposures using standard assumptions and unit exposure data. The unit exposure data were generally taken from PHED and ORETF studies for professional lawn care operators. All of the mixer/loader MOEs exceed the target of 100 with single layer PPE (i.e., baseline clothing with gloves) and are not of concern to HED. The MOEs for applicators are above 100 with baseline or single-layer PPE. The MOEs for the mixer/loader/applicators are acceptable with single-layer PPE and the MOEs for the flaggers are acceptable with baseline PPE. Dicamba labels typically require baseline clothing with waterproof gloves.

Occupational Post-Application Risk

Post-application exposure to re-entry workers may occur to workers performing activities in treated fields. In the last occupational exposure assessment (for the RED), post-application activities in field corn were assessed. The highest transfer coefficient (TC) for field corn is 400 cm^2/hr for weeding and scouting activities in medium mature plants. Post-application activities in sweet corn are expected to result in higher exposure than those for field corn and include hand harvesting and corn detasseling, which have a TC of 17,000 cm^2/hr. Risk for sweet corn detasseling and hand harvesting result in an MOE of 130 on day 0, which is not of concern to HED. All other post-application MOEs are above the target MOE of 100 on Day 0.

The Distinct® label (EPA Reg. No. 7969-150) lists an REI of 12 hours. Dicamba is listed as Acute Toxicity Category II for Primary Eye Irritation and Primary Skin Irritation. The interim WPS REI for compounds exhibiting Toxicity Category II effects for primary eye and skin irritation is 24 hours (40 CFR Part 156 § 156.208 (c) (1) and (2). **HED requests confirmation of the basis for a 12-hour REI for this product.**

9.0 Data Needs and Label Recommendations

9.1 Toxicology

No data needs.

9.2 Residue Chemistry

Additional sweet corn field residue trials.

Revised Section F.

9.3 Occupational and Residential Exposure

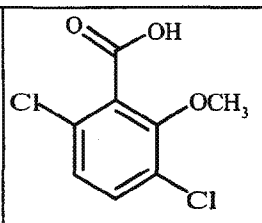
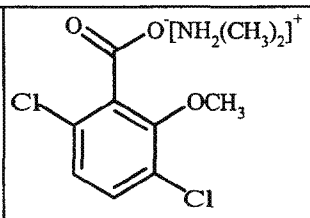
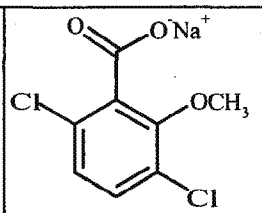
HED recommends that RD clarify the appropriate REI for dicamba.

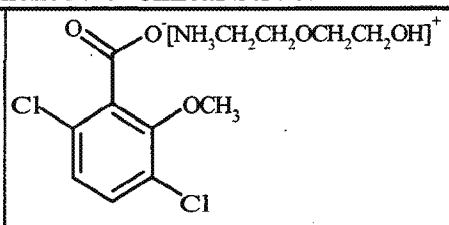
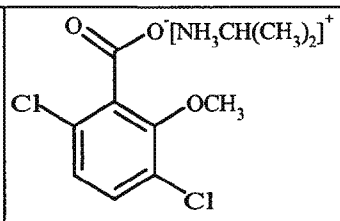
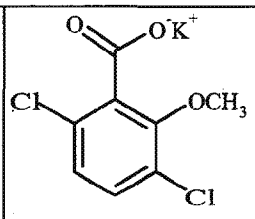
Attachment 1: Toxicity Profile for Dicamba

Attachment 2: Chemical Structures for Dicamba and its Salts

Attachment 1: Toxicity Profile for Dicamba		
Guideline No./ Study Type/	**MRID Nos. Doses/Classification**	**Results**
870.3100 Subchronic Oral - Rat	44623101 (1997) (0, 500, 3000, 6000, 12000 ppm) M:0,40.1,238.7,479.4,1000 mg/kg/day F:0,43.2,266.4,535.6,1065.3 mg/kg/day Acceptable/Guideline	NOAEL= 479.4/535.6 mg/kg/day(M/F). LOAEL= 1000/1065.3 mg/kg/day (M/F) based on clinical signs, decr. body weight gains, incr. liver wt and incr. hepatocyte hypertrophy and hepatocellular pigmentation.
870.3200 28-Day dermal toxicity - Rat	45814501 (2002) 0,30,300,1000 mg/kg/day (M/F) Acceptable/Guideline	NOAEL= 1000 mg/kg/day (HDT) LOAEL= not determined.
870.3700a Prenatal developmental - Rat	00084024 (1981) 0,64,160,400 mg/kg/day (GD 6-19) Acceptable/Guideline	**Maternal**: NOAEL= 160 mg/kg/day; LOAEL= 400 mg/kg/day based on Incr. mortality, clinical signs, decr. body weight gains, decr. food consumption. **Developmental**: NOAEL= 400 mg/kg/day (HDT), LOAEL not established.
870.3700b Prenatal developmental - NZW Rabbit	42429401 (1992) 0,30,150,300 mg/kg/day (GD 6-18) Range-finding: 0,62.5,125,250,500 mg/kg/day (GD 6-18) Acceptable/Guideline	**Maternal**: NOAEL= 62.5 mg/kg/day, LOAEL= 150 mg/kg/day based on incr. abortion, clinical signs (decr. motor activity, ataxia). **Developmental**: NOAEL= 62.5 mg/kg/day, LOAEL= 150 mg/kg/day based on incr. abortion.
870.3800 Reproduction and fertility effects - Rat	43137101 (1993) (0,500,1500,5000 ppm) M: 0,40,122,419 mg/kg/day F: 0,45, 136, 450 mg/kg/day Acceptable/Guideline	**Parental/Systemic:** NOAEL= 122/136 mg/kg/day (M/F); LOAEL= 419/450 mg/kg/day (M/F) based on clinical signs (slow righting reflex). **Reproductive:** NOAEL=122 mg/kg/day; LOAEL= 419 mg/kg/day based on delayed sexual maturation in F1 males. **Offspring:** NOAEL=45 mg/kg/day; LOAEL= 136 mg/kg/day based on impaired pup growth (decr. pup weights) in all generations during lactation period.
870.4200a Chronic Toxicity/ Carcinogenicity -Rat	00146150 (1985) (0,50,250,2500 ppm) M: 0,2,11,107 mg/kg/day F: 0,3,13,127 mg/kg/day Acceptable/Guideline	NOAEL= 107/127 mg/kg/day (M/F), LOAEL was not established. Not carcinogenic. The study is considered adequate for evaluating the carcinogenic potential.
870.4100b Chronic toxicity - dog	40321102 (1986) (0,100,500,2500 ppm) 0,2,11,52 mg/kg/day Acceptable/Guideline	NOAEL=52 mg/kg/day (HDT).

Attachment 1: Toxicity Profile for Dicamba		
Guideline No./ Study Type/	**MRID Nos. Doses/Classification**	**Results**
870.4200b Carcinogenicity - mouse	40872401 (1988) (0,50,150,1000,3000 ppm) M: 0,5.5,17.2,108,358 mg/kg/day F: 0,5.8,18.8,121,354 mg/kg/day Acceptable/Guideline	NOAEL=358/354 mg/kg/day (M/F), LOAEL was not established. Not carcinogenic. The study is considered adequate for evaluating the carcinogenic potential.
870.5100 Gene Mutation Salmonella typhimurium	00143001(1979) Acceptable/Guideline	Not mutagenic.
870.5395 Chromosome aberration (CHO)	40321101 (1986) Acceptable/Guideline	Chromosome aberrations were not induced in a cultured CHO cells at concentrations of 2330, 1170, 590, and 300 µg/mL either with or without S-9 activation.
870.5550 Unscheduled DNA synthesis (UDS)	00143001 (1979) Acceptable/Guideline	No evidence of UDS at levels 0.1 to 3000 µg/mL.
870.6200 Acute Neurotoxicity - Rat	42774104 (1993) 0,300,600,1200 mg/kg Acceptable/Guideline	NOAEL was not established, LOAEL=300 mg/kg based on severe neurological signs (impaired respiration, rigidity upon handling, prodding, or dropping, impaired gait and righting reflex in both sexes.
870.6200 Subchronic neurotoxicity - Rat	43245210 (1994) (0,3000,6000,12000 ppm) M:0,197.1,401.4,767.9 mg/kg/day F: 0,253.4,472.0,1028.9 mg/kg/day Acceptable/Guideline	NOAEL= 401.4/472.0 mg/kg/day (M/F); LOAEL= 767.9/1028.9 mg/kg/day (M/F) based on rigidity body tone, slightly impaired righting reflex and gait.
870.6300 Developmental Neurotoxicity -Rat	Not Required.	
870.7485 Metabolism	00028261(1967) Acceptable/guideline	Rapidly absorbed and excreted in urine and feces. Dicamba is not metabolized or bioaccumulation.

Attachment 2: Chemical Structures for Dicamba and its Salts	
PC Code 029801	
Chemical structure	
Common name	Dicamba acid
Molecular Formula	$C_8H_6Cl_2O_3$
Molecular Weight	221.04
IUPAC name	3,6-dichloro-*o*-anisic acid
CAS name	3,6-dichloro-2-methoxybenzoic acid or 2-methoxy-3,6-dichlorobenzoic acid
CAS #	1918-00-9
PC Code 029802	
Chemical structure	
Common name	Dicamba dimethylamine salt (DMA salt)
Molecular Formula	$C_{10}H_{13}Cl_2NO_3$
Molecular Weight	266.1
CAS #	2300-66-5
PC Code 029806	
Chemical structure	
Common name	Dicamba sodium salt (Na salt)
Molecular Formula	$C_8H_5Cl_2NaO_3$
Molecular Weight	243.0
CAS #	1982-69-0
PC Code 128931	

Attachment 2: Chemical Structures for Dicamba and its Salts	
Chemical structure	
Common name	Dicamba diglycolamine salt (DGA salt)
Molecular Formula	$C_{12}H_{17}Cl_2NO_5$
Molecular Weight	326.18
CAS #	104040-79-1
PC Code 128944	
Chemical structure	
Common name	Dicamba isopropylamine salt (IPA salt)
Molecular Formula	$C_{11}H_{15}Cl_2NO_3$
Molecular Weight	280.15
CAS #	55871-02-8
PC Code 129043	
Chemical structure	
Common name	Dicamba potassium salt (K salt)
Molecular Formula	$C_8H_5Cl_2KO_3$
Molecular Weight	259.1
CAS #	10007-85-9

13544

R158198

Chemical: Dicamba

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